[0152] The compounds identified from the docking modeling were tested for their ability to inhibit PKCδI. 3T3L1 cells were plated in 60 mm dishes and differentiated. PKCδI regulates cell cycle during differentiation of pre-adipocytes to adipocytes. The inhibitors were added on day 1 of differentiation during mitotic clonal expansion when PKCδI expression is high (18). After 24 h, the cells were harvested and western blot analysis was performed on whole cell lysates. Using a C-terminal PKCδ antibody, it was demonstrated that the compounds 5139627, 5320091, 72950115, 28578828, 61397826 and 43844983 can inhibit the cleavage and release of the PKCδI catalytic domain. The compounds did not decrease PKCδII expression. The results demonstrate decreased phosphorylation of myelin basic protein, a known PKCδI substrate in the presence of the compounds 5320091, 72950115, 28578828, 61397826 and 43844983.

[0153] Next, compounds 5139627, 5320091, 72950115, 28578828, 61397826 and 43844983 were tested on mature adipocytes. The inhibitors were added on day 6 of differentiation when the adipocytes are lipid laden. After 24 h, the cells were harvested and western blot analysis was performed on whole cell lysates. Results are shown in FIG. **2**. The results demonstrate decreased phosphorylation of myelin basic protein, a known PKCδI substrate in the presence of the compounds 5139627, 5320091, 72950115, 28578828, 61397826 and 43844983. Using a C-terminal PKCδ antibody, it was demonstrated that the compounds 5139627, 5320091, 72950115, 28578828, 61397826 and 43844983 inhibited the cleavage and release of the PKCδI catalytic domain. The compounds did not decrease PKCδII expression. Compound 43844983 appeared to completely inhibit PKCδI cleavage and phosphorylation of MBP in both pre-adipocytes and mature adipocytes; the other compounds inhibited cleavage of PKCδI and phosphorylation of MBP by over 85%.

[0154] Next, in vitro kinase assays were performed with recombinant proteins PKCδI and SC35 (as substrate) in a kinase buffer containing phosphatidyl serine and ATP; with and without 10 nM 5139627, 28578828 (30 min incubation prior to assay). Representative results are shown in FIG. **3**. It was demonstrated that at least 5139627, 28578828, can specifically inhibit PKCδI activity.

[0155] Next it was validated that 5139627 does not affect the activity of other PKCs, and thus can specifically inhibit PKCδI. Briefly, a Protein Kinase C (PKC) kinase activity kit was used and a colorimetric assay (ENZO; run in triplicate) was performed. Relative kinase activity was calculated as (average absorbance of PKC isozyme−Average absorbance of blank)/quantity of pure kinase used per assay. FIG. **4** demonstrates the results from a PKC kinase activity assay, which demonstrates that at least compound 5139627 has specificity for PKCδI and that other PKC isozyme activities were not inhibited by 5139627.

[0156] A WST-1 assay performed using obese adipocytes treated with 513627 to evaluate toxicity of compound 513627. Briefly, obese adipocytes were treated with 10 nM of compound 513627 and a WST-1 assay for cell viability was performed. FIG. **5** represents data from four experiments. The data demonstrates that compound 513627 did not appear to cause cellular toxicity (FIG. **5**).

[0157] In obesity, TNFα promotes inflammation and apoptosis of adipocytes. The data can demonstrate that TNFα cleaves PKCδI. Briefly, about 100 ng TNFα was added to lean adipocytes along with about 10 nM 5139627 for 24 h. Simultaneously, obese adipocytes were treated with 10 nM 5139627 for 24 h. Last, obese adipocytes were treated with about 10 nM of compound 5139627. Expression of pSC35, phosphor-myelin basic protein (pMBP) were analyzed via western blot. B-actin expression was used as a control. Results are demonstrated in FIG. **6**, which shows representative data from four experiments.

[0158] Additionally, adipocytes were isolated from lean or DIO mice. Expression of TNFα, PKCδI_F, PKCδI_C, pSC35, and β-Actin (control) was analyzed via western blotting. Results are demonstrated in FIG. **7**, which shows a representative blot from six experiments (each blot shows data from 2 mice). The results can indicate that PKCδI cleavage of its C-terminal domain (necessary to mediate its pro-apoptotic and pro-inflammatory action) is increased in obesity.

[0159] The C-terminal fragment of PKCδI phosphorylates its substrates that mediate expression of pro-apoptotic proteins. For a functional read-out, an assay was designed to measure: (1) Bcl-xL switching to its pro-apoptotic variant Bcl-xS and (2) Caspase9b switching to its pro-apoptotic variant caspase 9a. Briefly, adipocytes were freshly isolated from human visceral adipose tissue of lean and obese donors (IRB #20295; lean BMI 22.1 and 23; obese BMI 43.7 and 44.3; non-diabetic, nonsmokers, non-cancer). Results are shown in FIG. **8**, and can demonstrate that obese adipocytes had greater expression of BclxS and caspase9a.

[0160] Additionally, adipocytes from the obese donor were treated with about 10-100 nM NP627 (compound 513627) for about 24 h (n=3). Expression of PKCδI_F, PKCδI_C, PKCδVIII, and β-Actin (control) were analyzed using western blotting. Results are shown in FIG. **9**, and can demonstrate that NP627 specifically inhibits cleavage of PKCδI; the alternatively spliced variant PKCδVIII is not inhibited by NP627.

[0161] Additionally, adipocytes from the obese donor were treated with about 10 nM of NP627 for about 24 h (n=3). Expression of Bxl-xL, Bxl-xS, caspase9a, andβ-actin (control) were analyzed using a PCR based technique (n=3). A representative PCR gel image is shown in FIG. **10**. The results can demonstrate that NP627 can decrease expression of Bxl-xS and caspase9a.

[0162] Additionally, apoptosis in adipocytes from an obese subject treated with NP627 was examined using flow annexin/PI cytometry (n=3). Results are shown in FIG. **11**. ***$p<0.001$, which is considered highly significant.

REFERENCES FROM EXAMPLE 1

[0163] 1. Parker, P. J., and Murray-Rust, J. (2004) PKC at a glance. *J Cell Sci* 117, 131-132

[0164] 2. Sampson, S. R., and Cooper, D. R. (2006) Specific protein kinase C isoforms as transducers and modulators of insulin signaling. *Mol Genet Metab* 89, 32-47

[0165] 3. Emoto, Y., Manome, Y., Meinhardt, G., Kisaki, H., Kharbanda, S., Robertson, M., Ghayur, T., Wong, W. W., Kamen, R., Weichselbaum, R., and et al. (1995) Proteolytic activation of protein kinase C delta by an ICE-like protease in apoptotic cells. *EMBO J* 14, 6148-6156

[0166] 4. Ghayur, T., Hugunin, M., Talanian, R. V., Ratnofsky, S., Quinlan, C., Emoto, Y., Pandey, P., Datta, R., Huang, Y., Kharbanda, S., Allen, H., Kamen, R., Wong, W., and Kufe, D. (1996) Proteolytic activation of